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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
|---|---|---|---|---|
| 10/075,823 | 02/12/2002 | Waldemar Debinski | 6460-41 | 8785 |

7590 12/19/2006

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| EXAMINER | |
|---|---|
| HUYNH, PHUONG N | |
| **ART UNIT** | **PAPER NUMBER** |
| 1644 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 12/19/2006 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/075,823 | DEBINSKI ET AL. | |
| | Examiner | Art Unit | |
| | Phuong Huynh | 1644 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *Three* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-14 and 18-43* is/are pending in the application.

4a) Of the above claim(s) *3-8 and 19-43* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,9-14 and 18* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 8/11/06 has been entered.

2. Claims 1-14 and 18-43 are pending.

3. Upon reconsideration, the search has been extended to cover claim 2.

4. Claims 3-8 and 19-43 stand withdrawn from further consideration by the examiner, 37 C.F.R. 1.142(b) as being drawn to non-elected inventions.

5. Claims 1, 9-14 and 18 (now claims 1-2, 9-14 and 18), drawn to a method for detecting a cancer in a brain tissue by analyzing the brain tissue sample for a VEGF-D protein marker using a probe that specifically binds to the VEGF-D protein, a probe is a VEGF-D antibody, are being acted upon in this Office Action.

6. Applicant's arguments with respect to claims 1, 9-11, 13-14 and 18 filed 8/11/06 have been considered but are moot in view of the new grounds of rejection.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

8. Claims 2, 13-14 and 18 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 2 recites the limitation "VEGF-D marker" in base claim 1. There is insufficient antecedent basis for this limitation in the claim. This is because base claim 1 recites "VEGF-D protein".

Claim 2 recites the limitation "...the step (B) of *analyzing*..." in base claim 1. There is insufficient antecedent basis for this limitation in the claim. This is because Base claim 1 step (B) recites contacting ....

The "step (B) of detecting" in claim 13 does not correspond to the step (B) in claim 1. Base claim 1 step (B) recites contacting..., not detecting. Further, the unlabeled antibody such as monoclonal antibody or polyclonal antibody in claim 13 step (B) has no antecedent basis in base claim 1. The antibody in base claim 1 is a labeled antibody and now the antibody becomes unlabeled.

Claim 13 recites the limitation "at least a portion" in base claim 1. There is insufficient antecedent basis for this limitation in the claim.

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 103(a) that form the basis for the rejections under this section made in this Office Action:

A person shall be entitled to a patent unless:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

10. This application currently names joint inventors. In considering Patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

11. Claims 1-2, 9-14 and 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Takano et al (Cancer Research 56: 285-2190, May 1996; PTO 1449) as evidence by Amalfitano et al (of record, Cancer Genet Cytogenet 116: 6-9, 2000; PTO 892) in view of Achen et al (Eur J Biochem 267: 2505-2515, 2000; PTO 1449) and US Pat No. 6,235,713 B1 (of record, filed Aug 1997; PTO 892).

Takano et al teach a method for detecting glioblastoma multiforme in a brain tissue sample from human patients (see entire document, page 2185, col. 2, Materials and Methods, in

particular). The reference method comprises the step of providing a brain tissue sample from brain tumor tissues and a sample from normal brain tissues (see page 2185, Col. 2, Tissue preparation, in particular), contacting the brain tissue sample with an antibody such as monoclonal antibody MV303 or polyclonal antibody that binds specifically to human $VEGF_{121}$ (see page 2185, col. 2, Immunocytochemistry, VEGF ELISA, in particular), detecting the overexpression of $VEGF_{121}$ in brain tissue (see page 2187, Fig. 2, in particular) and correlating the overexpression of $VEGF_{121}$ in tumor brain tissue with glioblastoma multiforme (see paragraph bridging page 2186 and 2187, Fig. 2A vs. Fig. 2E, Fig. 1, in particular). Takano et al also teach comparing the quantity of expression of VEGF121 with a sample known to express detectable levels of VEGF such as menigioma (positive control) and a sample known not to express detectable levels of the $VEGF_{121}$ such as normal brain tissue (negative control) (see page 2186, Table 1, Fig. 1, in particular). Takano et al teach VEGF is a useful maker and measurable elements of glioblastoma angiogenesis; it is possible that measurement of VEGF and other angiogenic peptides in tissue together with the measurement of neovascularization in the brain tumor itself, may be used to improve the management of patients with brain tumors (see abstract, page 2189, col. 2, last paragraph, in particular). As evidence by the teachings of Amalfitano et al teach that glioblastoma multiforme cell exhibited abnormal ploidy for chromosome X (see page 6, col. 1, in particular).

The claimed invention differs from the teachings of the references only in that the method of detecting wherein the antibody is labeled and binds specifically to human VEGF-D protein, or a native human VEGF-D protein or homology domain of human VEGF-D instead of $VEGF_{121}$.

Achen et al teach various monoclonal antibodies such as VD1, VD2, VD3 and VD4 that bind specifically to fully processed bioactive homology domain (VHD) of human VEGF-D (VEGF-DΔNΔC), which is a proteolytic cleavage product (see entire document, paragraph bridging pages 2508-2509, in particular). All four of the reference mAbs also bind to the full-length unprocessed (native) human VEGF-D, especially mAb VD1 (see page 2508, col. 2, page 2505, col.1, last paragraph, n particular). Achen et al teach VEGF-D contributes to the development of blood vessels and lymphatic vessels during tumor growth (see page 2505, col. 2, last paragraph, in particular). Achen et al teach antibodies to VEGF-D will be powerful tools for analysis of the biological functions of VEGF-D and its role in VEGF-D in tumor angiogenesis as well as other inappropriate angiogenesis (see abstract, page 2513, col. 1 second and third paragraphs, in particular).

The '713 patent teaches a method of detecting VEGF-D in a biological sample comprising the steps of contacting a sample with a probe such as labeled polyclonal or monoclonal that binds specifically to human VEGF-D (see col. 5, lines 56-67, col. 6, lines 1-10, col. 6, lines 66-67 bridging col. 7, lines 1-7, in particular). The reference VEGF-D is a native VEGF-D protein (see col. 19, lines 34-42, VEGFD full FLAG, in particular) and could be proteolytic cleaved to form the VEGF-D homology domain (see col. 19, line 25, VEGFDΔNΔC, in particular). The '713 patent teaches VEGF-D is located on the X chromosome in band p22.1 (see col. 24, lines 1-8, in particular) and is useful as a clinical diagnostic marker in cancer biopsy specimens and is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular). The '713 patent further teaches a method of detecting the aberrations in VEGF-D located on the X chromosome (see col. 7, lines 40-43, in particular).

Therefore, it would have been obvious to one of ordinary skill in the art at the time the invention was made to detect glioblastoma multiforme from brain tissue sample as taught by Takano by substituting the monoclonal or polyclonal antibody that binds to $VEGF_{121}$ as taught by Takano et al for the labeled monoclonal antibody such as VD1 that binds to human VEGF-D protein, or a native human VEGF-D protein (full-length) or homology domain of human VEGF-D (processed) as taught by Achen et al or the polyclonal or monoclonal antibody that binds to the human VEGF-D as taught by the '713 patent where glioblastoma multiforme cells are known to exhibit abnormal ploidy for chromosome X as taught by Amalfitano et al. From the combined teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed invention.

One having ordinary skill in the art would have been motivated to do this because Takano et al teach VEGF is a useful maker for glioblastoma multiforme (GBM) angiogenesis (see abstract, page 2189, col. 2, last paragraph, in particular) and known to exhibited abnormal ploidy for chromosome X as taught by Amalfitano et al. Achen et al teach antibodies to VEGF-D will be powerful tools for analysis of the biological functions of VEGF-D and its role in tumor angiogenesis as well as other inappropriate angiogenesis (see abstract, page 2513, col. 1 second and third paragraphs, in particular). The '713 patent teaches VEGF-D is located on the X chromosome in band p22.1 (see col. 24, lines 1-8, in particular) and VEGF-D is useful as a clinical diagnostic marker in cancer biopsy specimens and VEGF-D detection using antibody is an indicator of future metastatic risk (see col. 6, lines 16-18, in particular).

12. No claim is allowed.

13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Phuong Huynh "NEON" whose telephone number is (571) 272-0846. The examiner can normally be reached Monday through Thursday from 9:00 a.m. to 6:30 p.m. and alternate Friday from 9: 00 a.m. to 5:30 p.m. A message may be left on the examiner's voice mail service. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571) 272-0841. The IFW official Fax number is (571) 273-8300.

14. Any information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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December 8, 2006